CONJUGATED ESTROGENS*

First Listed in the *Fourth* and *Fifth Annual Report on Carcinogens*

CARCINOGENICITY

Conjugated estrogens are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans (IARC V.21, 1979). In two case-control studies, the use of intravaginal estrogen creams was reported to induce increased incidences of endometrial tumors. Cases of liver tumors, including a hepatic adenoma in one woman and a hemangioendothelial sarcoma in one man, have been reported to be associated with use of noncontraceptive estrogens (IARC V.21, 1979; IARC S.4, 1982). In another case-control study, the use of hormones during the mother's pregnancy increased the risk of the development of testicular cancer (tumors included embryonal cell carcinomas, seminomas, teratomas, choriocarcinomas, and interstitial cell carcinomas). An IARC Working Group reported that there is conflicting evidence linking conjugated estrogen use with breast cancer (IARC S.4, 1982).

An IARC Working Group reported that there is limited evidence of carcinogenicity of conjugated estrogens in experimental animals (IARC S.4, 1982; IARC S.7, 1987). The IARC Working Group reported that data from a study in rats were inadequate to evaluate the carcinogenicity of conjugated estrogens (IARC S.4, 1982). When implanted subcutaneously in pellet form, equilin induced renal tumors in castrated male hamsters (IARC S.7, 1987).

PROPERTIES

Conjugated estrogens are an amorphous mixture containing naturally occurring forms of mixed estrogens, principally sodium estrone sulfate (CAS No. 438-67-5), sodium equilin sulfate (16680-47-0), and piperazine estrone sulfate (7280-37-7), a synthetic conjugated estrogen. Conjugated estrogens generally occur as buff-colored powders that are soluble in water. The sodium equilin sulfate component is unstable in the presence of light and air. Piperazine estrone sulfate occurs as a white-to-yellowish-white crystalline powder that is slightly soluble in water, ethanol, chloroform, acetone, methylene chloride, mineral oil, and sesame oil; soluble in sodium hydroxide and propylene glycol; and practically insoluble in diethyl ether, benzene, and isopropyl alcohol. Conjugated estrogens are available in the United States as a USP grade containing 90% to 110% active ingredient; piperazine estrone sulfate is available domestically as an NF-grade containing 97% to 103% active ingredient.

USE

Conjugated estrogens are used as a prescription drug to treat symptoms of menopause, vulvar dystrophies, female hypogonadism, and dysfunctional uterine bleeding. They are also used for treatment following ovariectomy, for chemotherapy of mammary carcinoma and prostate carcinoma, and for prevention of postpartum breast engorgement. Additionally, conjugated estrogens have been used in cosmetic preparations (IARC V.21, 1979).

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* There is no separate CAS Registry Number assigned to conjugated estrogens.

PRODUCTION

The USITC identified one company producing an undisclosed amount of conjugated estrogens from 1975 through 1994 (IARC V.21, 1979; USITC, 1986-1991, 1993-1995). In 1978, 2,000 lb of all estrogens were produced in the United States. There was one producer of conjugated estrogens and one producer of piperazine estrone sulfate in 1978 (USITC, 1979). In 1975, U.S. production of 14 estrogen and progestin substances, including conjugated estrogens, amounted to about 23,000 lb. Commercial production of conjugated estrogens in the United States was first reported in 1968, although production of natural equine estrone was reported in 1959. Commercial production of piperazine estrone sulfate was first reported in the United States in 1950 (IARC V.21, 1979). No data on imports or exports of conjugated estrogens were available.

EXPOSURE

The primary routes of potential human exposure to conjugated estrogens are ingestion, injection, dermal contact, and inhalation. For medical use, oral administration has been generally in a cyclic regimen every day for 3 weeks followed by 1 week without. Dosage ranged from 1.25 mg/day for the treatment of vulvar dystrophies, to 10 mg three times per day for chemotherapy of mammary carcinoma. For dysfunctional uterine bleeding, conjugated estrogens may be administered in an intramuscular or intravenous dose of 25 mg, repeated within 6-12 hr if necessary. Piperazine estrone sulfate may be administered orally in doses of 1.5 mg per day for treatment of symptoms of the climacteric and following ovariectomy, up to 4.5 mg every 4 hr for a total of 5 doses for the prevention of postpartum breast engorgement. Unspecified estrogens, believed to include substances such as conjugated estrogens, have been used in cosmetic preparations, including hormonal skin preparations (at levels of less than 0.1%-5%), moisturizing lotions (1%-5%), wrinkle-smoothing compounds, hair conditioners, hair straighteners, shampoos, and grooming aid tonics (< 0.1%). Workers involved in the manufacture of products and processing of pharmaceuticals containing conjugated estrogens are potentially exposed to these compounds through inhalation, ingestion, and dermal contact. Conjugated estrogens are naturally occurring substances excreted in the urine of pregnant mares. Piperazine estrone sulfate, however, is not known to occur naturally (IARC V.21, 1979).

REGULATIONS

CPSC has determined that conjugated estrogen tablets, when dispensed in mnemonic packages containing up to 32.0 mg of the drug and no other substances requiring special packaging, are prescription drugs that do not require special packaging. Because conjugated estrogens are used as pharmaceuticals and in low quantities relative to other chemicals, they are not regulated by EPA. However, there may be a small pollution problem relative to hospital wastes. FDA regulates conjugated estrogens under the Food, Drug, and Cosmetic Act (FD&CA) as an over-the-counter drug for human and animal use. FDA has ruled that estrogens for general use must carry patient and physician warning labels concerning use, risks, and contraindications. OSHA also regulates conjugated estrogens as chemical hazards in laboratories under the Hazard Communication Standard. Regulations are summarized in Volume II, Table A-18.